REMARKS

Claims 2-17, 19, 20, 22, 24-33, 35-38, 40-47, 49-54, and 68-83 are pending and under consideration. With this Amendment, Claims 2-17, 19, 20, 22, 24-27, 29-33, 35-38, 40-47, 49-54 and 68-83 are being amended, Claim 28 is being canceled, without prejudice against its reintroduction into this or one or more timely filed continuation, divisional or continuation-in-part applications, and Claims 84-88 are being newly added. Thus, after entry of this Amendment, Claims 2-17, 19, 20, 22, 24-27, 29-33, 35-38, 40-47, 49-54 and 68-88 are pending and under consideration. The amendments of the claims and the various rejections raised in the Office Action are discussed in more detail, below.

The Amendments of the Claims

Claims 2-17, 19, 20, 22, 24-27, 29-33, 35-38, 40-47, 49-54 and 68-83 have been amended for clarity. Claims 84 and 85 recite limitations that were deleted from Claims 68 and 71, from which they depend. Support for Claims 86, 87, and 88 can be found at paragraphs 67, 74, 77, 86, 116-125, and 143-172. No new matter is added by virtue of the amendments.

Rejection Under 35 U.S.C. § 103(a)

Claims 2, 3, 8, 10, 10 [sic], 14-17, 19, 22, 24, 28, 30, 33-38, 40-47, 49-54, and 68-77 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,207,752 to Sorenson et al. ("Sorenson et al.") in view of Palmeri et al. and U.S. Patent No. 6,436,091 to Harper et al. ("Harper et al."). According to the Patent Office ("Office"), Sorenson et al., Palmeri et al. and Harper et al. in combination suggest to the artisan of ordinary skill a method of treatment by optimizing interferon doses by administering a first level and then administering a second level using an internal pump that meets all of the limitations of the claimed invention. The Office contends that the motivation to combine the references is found in Palmeri et al. which disclose a problem that can be solved by Sorenson et al. and Harper et al. Applicant traverses the rejection.

Applicant continues to maintain that the cited art does not support an obviousness rejection. Section 103(a) precludes the grant of a patent only if "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains" 37 U.S.C. § 103(a). The Office bears the initial burden of establishing a case of *prima facie* obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); *In re Fine*, 5 USPQ2d 1956, 1958 (Fed. Cir. 1998);

MPEP § 2142. If the Office does not establish a *prima facie* case, the Applicant is under no obligation to submit evidence of nonobviousness, and the rejection must be withdrawn. *Id.*

To establish a proper *prima facie* case, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation that the modification or combination would be successful. Third, the prior art reference (or references when combined) must teach all the limitations of the rejected claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based upon Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow*, 5 USPQ2d 1529 (Fed. Cir. 1988); MPEP § 2142.

Applicant respectfully asserts that the references alone or in combination do not teach or suggest all of the claim limitations.

Independent Claim 68 is drawn to a method of treating an interferon-responsive disorder in a subject comprising determining a well-tolerated, therapeutic pharmacokinetic profile for interferon therapy in a subject by administration of one or more interferons formulated for short-term delivery to the subject and monitoring the subject for therapeutic and adverse effects; and administering to the subject using at least one internally presented, not externally programmable pump one or more interferons formulated for long-term delivery in which the interferons are released from the pump at a rate that substantially achieves the pharmacokinetic profile during long-term delivery.

In contrast to Claim 68, Sorenson et al. provide a subject with an initial peak level of drug concentration that is followed by lower maintenance levels. Thus, the initial drug concentration of Sorenson et al. is reduced and is not substantially achieved over the period of long-term delivery. The therapeutic effect of the initial drug concentration of Sorenson et al. also is not considered in the selection of the maintenance level of drug that is administered or the formulation that is used. Therefore, Sorenson et al. at least do not teach or suggest achieving a well-tolerated, pharmacokinetic profile using a long-term delivery formulation, wherein the well-tolerated, therapeutic pharmacokinetic profile is determined using a short-term delivery formulation. In addition, the pump of Sorenson et al. is externally programmable whereas the pump of Claim 68 is not.

The secondary reference, Palmeri et al., does not cure the deficiencies of Sorenson et al. Palmeri et al. disclose the results of a study designed to identify the maximally tolerated dose of recombinant alpha interferon-2a (raIFN-2a) in combination with 5-fluorouracil (5FU). In Palmeri et al., escalating

doses of raIFN-2a were administered to patients subcutaneously and the patients were monitored for adverse effects but were not monitored for therapeutic effects. Palmeri et al. state on page 330 that "the maximally tolerated dose of raIFN-2a is 9×10^6 IU given subcutaneously three times/week" and the "combination [of 5FU and raIFN-2a] is now ready to be tested. . . in order to evaluate its therapeutic activity." Therefore, in contrast to Claim 68, Palmeri et al. do not disclose a well-tolerated, therapeutic pharmacokinetic profile for interferon therapy. Palmeri et al. state that the therapeutic effect of their selected dose of raIFN-2a is unknown. Palmeri et al. also disclose subcutaneous injection of raIFN-2a and do not teach or suggest the use of an internally presented, not externally programmable pump or the use of a long-term formulation to achieve a well-tolerated, therapeutic pharmacokinetic profile that is determined using interferon formulated for short-term delivery.

The third reference, Harper et al., discloses an implantable pump for delivering a pharmaceutical agent to a patient but does not teach or suggest determining a well-tolerated, therapeutic pharmacokinetic profile for interferon therapy in a subject using one of more interferons formulated for short-term delivery and administering to the subject using at least one internally presented, not externally programmable pump one or more interferons formulated for long-term delivery in which the interferons are released from the pump at a rate that substantially achieves the pharmacokinetic profile during long-term delivery.

Therefore, Applicant respectfully asserts that the references do not teach or suggest all the limitations of Claim 68 and do not support a legal conclusion of obviousness. Sorenson et al. disclose administering from an externally programmable pump an arbitrarily selected high drug dose followed by an arbitrarily selected lower maintenance dose. Palmeri et al. disclose the identification of a maximally tolerated dose of interferon by subcutaneous administration of interferon and monitoring the subjects of the study for adverse effects. Palmeri et al. do not teach or suggest long-term delivery of interferon using an internally presented pump that is not externally programmable. Harper et al. disclose an implantable pump but has no teaching or suggestion regarding interferon formulated for long-term delivery to achieve a well-tolerated therapeutic pharmacokinetic profile determined by administration of interferon formulated for short-term delivery. Therefore, the references alone or in combination at least do not teach or suggest determining a well-tolerated, therapeutic pharmacokinetic profile for interferon therapy using one or more interferons formulated for short-term delivery and administering to a subject one or more interferons formulated for long-term delivery that are released from at least one internally presented, not externally programmable pump at a rate that substantially achieves the well-tolerated and therapeutic pharmacokinetic profile.

The Office also contends that the motivation to combine the references can be found in Palmeri et al. because Palmeri et al. disclose a problem that can be solved by the method of Sorenson et al. and Harper et al. However, the Office has not cited a problem of Palmeri et al. that can be solved by application of the devices of Sorenson et al. and Harper et al. Palmeri et al. disclose a study to determine a maximally tolerated dose of subcutaneously administered raIFN-2a which Palmeri et al. identify on page 330. Therefore, the Office merely makes an unsupported conclusion regarding the problem of Palmeri et al. and its resolution by the application of Sorenson et al. and Harper et al. Applicant respectfully asserts the references either alone or in combination do not teach or suggest all the claim limitations and therefore there can be no motivation to combine them to arrive at the claimed invention. Therefore, in making its rejection, the Office apparently has used impermissible hindsight analysis to combine the references to arrive at the claimed invention. Using Applicant's disclosure as a guide, the Office identified aspects of the references it believes to be claim limitations and has used unsupported assertions regarding their combination to support its conclusion of obviousness.

Applicant submits that the arguments put forth above also apply in traversing the rejection of independent Claims 41 and 73. Therefore, Applicant respectfully asserts that the rejection under 35 U.S.C. § 103(a) is improper and respectfully requests that it be withdrawn.

Claims 4-7, 9, 12, 13, 20, 25-27, 29, 32, 33, and 78-83 stand rejected under 35 U.S.C. § 103(a) as being obvious over Sorenson et al. in view of Palmeri et al. and Harper et al. in further view of Johnson et al. According to the Office, it would be obvious to combine the teachings of Sorenson et al., Palmeri et al. and Harper et al. with Johnson et al. to optimize doses for the treatment of diseases. The Office contends that one of ordinary skill would be motivated to do so because Palmeri et al. and Johnson et al. disclose that interferons have toxic side effects. Applicant traverses the rejection.

Applicant respectfully points out that each of the above claims are dependent claims. Since the obviousness rejection is improper with respect to the independent claims due to the failure of the references alone or in combination to teach or suggest all the claim limitations, Applicant maintains that the rejection of the dependent claims in view of Sorenson et al., Palmeri et al., Harper et al., and Johnson et al. is also improper. Johnson et al., which disclose various types of interferons and their use in the treatment of disease, do not cure the deficiencies of Sorenson et al., Palmeri et al. and Harper et al. Therefore, as stated above, the references do not teach or suggest all the claim limitations and can not support a legal conclusion of obviousness. Therefore, Applicant respectfully submits that the rejection under 35 U.S.C. § 103(a) is improper and respectfully requests that it be withdrawn.

Claims 11 and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sorenson et al. in view of Palmeri et al., Harper et al., and Johnson et al. in further view of U.S. Patent No. 4,837,079 to Kwan ("Kwan"). According to the Office, Kwan discloses mixtures of interferon comprising thimerosol which retard bacterial growth. The Office's interpretation of Sorenson et al., Palmeri et al., Harper et al., and Johnson et al. is summarized above. Applicant traverses the rejection.

Applicants maintain that the rejection is meaningless in that Kwan's formulations of interferon and thimerosol are not relevant to the scope of Claims 11 and 31. Claim 11 is drawn to the method of Claim 2, wherein the short-term formulation and the long-term formulation are the same. Claim 31 is drawn to the method of Claim 22, wherein the short-term formulation and the long-term formulation are different. Neither claim and the claims from which they depend recite thimerosol. Therefore, the disclosure of Kwan is irrelevant.

Kwan's disclosure of interferon/thimerosol mixtures also does not cure the deficiencies of Sorenson et al., Palmeri et al., Harper et al., and Johnson et al. Therefore, these references in combination with Kwan do not teach or suggest all the limitations of the independent claims. Therefore, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

The claims are believed to satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly requested.

No fees beyond those set forth in 37 CFR § 1.17(a)(3) for extension of time pursuant to 37 CFR § 1.135(a) for reply within the third month by a small entity are believed to be due in connection with this Amendment. However, the Commissioner is authorized to charge any additional fees that may be required, or credit any overpayment, to Dechert LLP Deposit Account No. 50-2778 **(Order No. 375608-004US (360890))**.

Respectfully submitted,

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